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# Combination of Immunotherapy and Radiotherapy—The Next Magic Step in the Management of Lung Cancer?



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Immune checkpoint inhibitors (ICIs), especially the anti-programmed death ligand 1 (anti-PD-L1), have revolutionized the treatment landscape of metastatic lung cancer. Most patients with metastatic NSCLC without a targetable driver mutation will receive first-line ICI, either as monotherapy or in combination with chemotherapy.<sup>1</sup> Atezolizumab (and in the near future, probably durvalumab) in combination with chemotherapy has become the first-line treatment for metastatic SCLC on the basis of the IMPower133 and CASPIAN trials, respectively.<sup>2,3</sup> Furthermore, once the results of the PACIFIC trial became known, adjuvant durvalumab became the standard of care for patients with stage III NSCLC that was not progressing after concurrent chemoradiation (CCRT).<sup>4</sup> Unfortunately, not all patients obtain long-term benefit with these treatments, and new treatment strategies are being explored to improve overall survival (OS).

A logical option is to combine (thoracic) radiotherapy with ICI because radiation up-regulates major histocompatibility complex class I antigens, increases tumor

antigen release, drives a polyclonal T-cell response, enhances CD8+ T-cell infiltration, limits T-cell exhaustion, modulates the immune environment, provokes an interferon gamma response, and can up-regulate PD-L1.<sup>5</sup> The PACIFIC trial was the first randomized phase III study to clinically validate these findings.<sup>4</sup> Preclinically, improvement in antitumor effects has been observed when radiotherapy is given concurrently with or immediately after anti-PD-L1, rather than sequentially.<sup>6</sup> The PACIFIC trial results, which suggested that the OS was better when durvalumab was given within 2 weeks after the end of CCRT, are, therefore, consistent with preclinical data.<sup>7</sup> Therefore, concurrent radiotherapy-ICI strategies are being tested in clinical trials. A possible drawback of thoracic radiotherapy (TRT) combined with ICI is the perceived increased risk of radiation pneumonitis. The two studies accompanying this editorial shed some more light on the safety and efficacy of concurrent TRT and anti-PD-L1 in metastatic SCLC and unresectable NSCLC, respectively.

Welsh et al.<sup>8</sup> evaluated in a classic phase I 3 plus 3 design increasing doses of pembrolizumab (maximum 200 mg) every 3 weeks combined with TRT (45 Gy per 15 daily fractions) administered sequentially after induction platinum-etoposide chemotherapy in extensive-stage

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SCLC.<sup>8</sup> TRT (30 Gy per 10 daily fractions) was investigated in the CREST study in patients with stage IV SCLC after induction chemotherapy and prophylactic cranial irradiation, showing no improvement in the primary end point, 1-year OS.<sup>9</sup> A dose of 45 Gy per 15 daily fractions is, therefore, not a standard schedule in stage IV SCLC. No dose-limiting toxicities were observed in the 33 patients who received per-protocol treatment either within the 35-day dose-limiting toxicity window or in continued follow-up. No grade 4 to grade 5 toxicity was observed, but two patients experienced grade 3 toxicity (one rash, one exacerbation of a preexisting unknown autoimmune disorder) although the authors reported them as being unrelated to treatment. The addition of TRT to pembrolizumab in this trial did not seem to increase immune-related toxicity because grade 3 to grade 5 immune-related toxicity was also around 10% in monotherapy anti-PD-L1 SCLC trials.<sup>10</sup> Objective response rate does not seem to improve with the addition of TRT, as the objective response rate was 12% in a single-arm phase II pembrolizumab maintenance trial<sup>11</sup> compared with 15% (measured by Immune-Related Response Criteria) in the current trial. More importantly, at a median follow-up of 7.3 months, the median progression-free survival (PFS) and OS were 6.1 (95% confidence interval: 4.1–8.0) and 8.4 months (95% confidence interval: 6.7–10.1), and 6-month PFS and OS rates were 50.3% and 76.5%, respectively. Although these results are similar to those of the CREST trial,<sup>9</sup> in the latter, patients were randomized after having achieved a remission after induction chemotherapy. In IMpower133, survival was higher, with a median OS of 12.3 months (atezolizumab) versus 10.3 months (placebo).<sup>3</sup>

The second study is the phase II DETERRED study from Lin et al.,<sup>12</sup> in which atezolizumab with CCRT was evaluated in unresectable NSCLC (15% stage IIB, others stage III). Patients had to be adequately staged with brain magnetic resonance imaging and <sup>18</sup>F-deoxyglucose-positron emission tomography-computed tomography scan and be eligible for CCRT. As a safety run-in, part 1 consisted of treatment with intensity-modulated radiation therapy (protons versus photons, 60–66 Gy in 30–33 daily fractions) concurrent with once-weekly carboplatin area under the curve 2.0 and paclitaxel 50 mg/m<sup>2</sup>, followed by two cycles of consolidation carboplatin area under the curve 6.0, paclitaxel 200 mg/m<sup>2</sup> and 1200 mg atezolizumab, followed by maintenance atezolizumab every 3 weeks for up to 1 year. Part 2 consisted of the same schedule, but atezolizumab was already introduced concurrently with the CCRT. The primary end points were safety and/or tolerability. Ten of the 15 patients in part 1 were treated with consolidation atezolizumab, and 30 of 37 patients in part 2 were treated with atezolizumab and CCRT. In both parts, 80% of the patients

experienced at least one episode of grade 3+ adverse events, which is slightly higher than that in CCRT without ICI<sup>13</sup> but is comparable with the phase II NICOLAS trial that assessed nivolumab given concomitantly with CCRT.<sup>14</sup> In the DETERRED study, 20% to 30% had grade 3+ immune-related toxicity, much higher than what was reported in the PACIFIC trial (3.4%).<sup>15</sup> However, the percentage of grade 3+ dyspnea per (radiation) pneumonitis was low (10% in part 1 and 3% in part 2), and comparable with the grade 3+ pulmonary adverse events in chemoradiation without ICI<sup>13</sup> and the PACIFIC (3.4% pneumonitis, 1.5% dyspnea) and NICOLAS trials (10% pneumonitis).<sup>14,15</sup> All immune-related toxicities were reversible with steroids and supportive care. Two patients in part 2 developed a recurrence before the start of consolidation therapy: one had a *Kirsten Rat Sarcoma Viral oncogene homolog (KRAS)/serine/threonine kinase 11 (STK11)* co-mutation, and the other had an *anaplastic lymphoma kinase (ALK)* rearrangement. With a median follow-up of 22.5 months (part 1) and 15.3 months (part 2), median PFS was 12.5 and 13.2 months, respectively, and median OS was 22.8 months and not reached (NR), respectively. PD-L1 status (evaluable in 34 of 40 patients) was not associated with recurrence. These survival data are similar to those of CCRT regimens without ICI, such as the PROCLAIM study.<sup>13</sup> Although difficult to compare with the PACIFIC trial<sup>4</sup> (survival measured from randomization after CCRT till death, instead from start of CCRT), the concurrent ICI-CCRT regimen does not strikingly improve survival.

## What Can We Learn From These Trials, and How Should We Proceed?

Both studies report that the combination of TRT and anti-PD-L1 is feasible. In contrast, survival in both trials does not seem to improve with the combination, compared with historical data. Better patient selection and biomarker research are needed, and these should be evaluated in well-designed randomized trials. Furthermore, for both studies, dose volume histogram constraints were not given, making the interpretation of radiotherapy toxicity difficult.

In metastatic SCLC, monotherapy ICI trials have reported disappointing results, with the suggestion that patients with a high PD-L1 expression or a high tumor mutational burden could benefit most. However, this has not been evaluated prospectively in a randomized trial.<sup>10</sup> Both the IMpower133 and the CASPIAN trials reported that the addition of ICI to platinum-doublet chemotherapy improved survival, although modestly.<sup>2,3</sup> In both trials, survival curves separated late, and patients who would benefit could not be identified.<sup>2,3</sup> It is possible that the addition of TRT to a chemo-ICI regimen can

make SCLC more immunogenic, but the optimal treatment sequence, radiation dose, and fractionation scheme should be evaluated prospectively. Many trials are ongoing (e.g., NCT02402920 and NCT02934503). Moreover, combinations of anti-CTLA4, anti-PD1, and TRT after completion of chemotherapy are also being evaluated (e.g., NCT03043599 and NCT0392370), of which the STIMULI trial (NCT02046733) has completed recruitment. A next step could be the addition of other immune-modulating drugs such as poly (ADP-ribose) polymerase (PARP)-inhibitors, as preclinically, PARP-inhibitors are radiosensitizers and immune modulators.<sup>16,17</sup> NCT03532880 is currently evaluating the safety of olaparib, a PARP-inhibitor, combined with radiotherapy; NCT03923270 is evaluating the safety of TRT followed by durvalumab with or without tremelimumab or olaparib.

In unresectable NSCLC, adjuvant durvalumab after CCRT has become the standard, but reliable patient-related factors or biomarkers to identify those who benefit most do not exist.<sup>4</sup> Only PD-L1 less than 1% was associated with the lack of OS benefit, but this was evaluated in an unplanned post hoc analysis requested by the European Medicines Agency (EMA). Molecular analysis in unresectable NSCLC would be of interest because in metastatic NSCLC, those with non-smoking-associated driver alterations such as *EGFR* and *ALK*, or those with *STK11* or *kelch like ECH associated protein 1 (KEAP1)* mutations often obtain very limited benefit from ICIs,<sup>18</sup> as was also seen in two patients in the DETERRED trial. Furthermore, patients with a driver alteration who are treated with a tyrosine kinase inhibitor after ICI seem to be at an increased risk of tyrosine kinase inhibitor-associated toxicity.<sup>19</sup> Finally, in the DETERRED trial, 22% of patients were treated with protons instead of photons, but differences in immune activation are not clear yet. NCT01993810 is evaluating protons versus photons in this setting.

Moreover, detection of progressive disease becomes a challenge in patients treated with CCRT and ICI, as both radiation and ICI can cause pneumonitis, which is sometimes difficult to distinguish from progressive disease. Alternative follow-up methods such as longitudinal circulating tumor DNA (ctDNA) or electronic nose (ENOSE) measurements would be of interest, as both ctDNA and ENOSE patterns are associated with outcome in ICI-treated metastatic NSCLC.<sup>20,21</sup>

Finally, long-term toxicities are not known yet. It is possible that patients treated with TRT-ICI will develop late pulmonary fibrosis or cardiac toxicity. The latter is interesting as PD-L1 is expressed on cardiomyocytes, and preclinically, excess cardiac mortality was found in mice treated with cardiac irradiation and an anti-PD-1.<sup>22</sup>

Different new strategies are currently being tested in unresectable NSCLC. Examples are neoadjuvant ICI followed by chemoradiation (e.g., NCT04085250); other immune agents added to chemoradiation (e.g., M7824 [NCT03840902], oleclumab or monalizumab [NCT03822351]); anti-CTLA4 added to chemoradiation plus anti-PD-1 (e.g., CheckMate73L [NCT04026412], or NCT03663166); and the addition of stereotactic body radiation to chemoradiation and durvalumab (e.g., NCT03589547). Toxicity and long-term outcomes are awaited.

In the end, ultimate success will be defined by the possibility of selecting those patients who are likely to have long-term survival in combination with a maintained or improved quality of life. More insight into the biological mechanisms underlying treatment resistance and toxicity is needed to improve the outcome for other patients. Biomarkers should be an integral part of any study, and prolonged detailed follow-up is needed.

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